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Jussi [FI/FI]; Soidintie 5 C, FIN-40630 JYVÄSKYLÄ (FI).

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(74) Agent: **KESPAT OY**; P.O.Box 601, FIN-40101 JYVÄSKYLÄ (FI).

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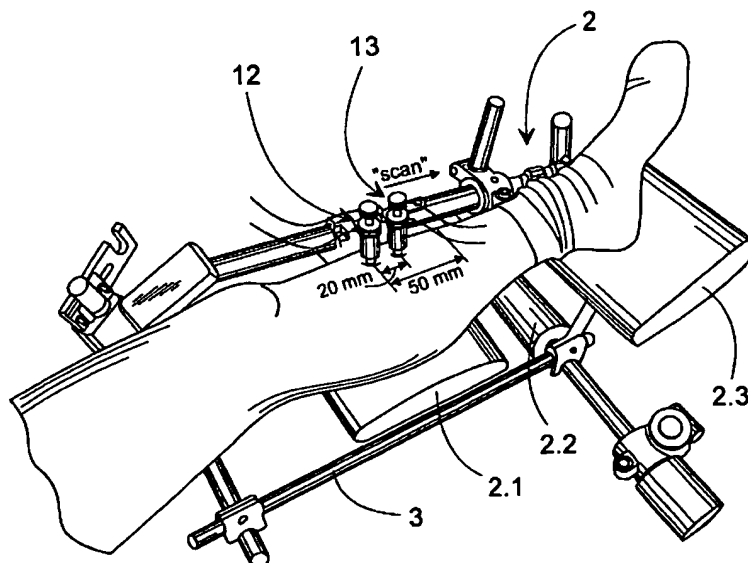
(71) Applicants and

(72) Inventors: **MOILANEN, Petro** [FI/FI]; Survontie 38 B 19, FIN-40520 JYVÄSKYLÄ (FI). **NICHOLSON, Patrick** [GB/GB]; 29 Gensing Road, ST LEONARDS ON SEA, Sussex TN390HE (GB). **CHENG, Shu Lin** [CN/FI]; Lehtokatu 8, FIN-40630 JYVÄSKYLÄ (FI). **TIMONEN,**

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(54) Title: A METHOD AND DEVICE FOR THE NON-INVASIVE ASSESSMENT OF BONES



(57) Abstract: A method for the in vivo non-invasive characterization of the material and architectural properties of a bone in which an ultrasonic wave is introduced into a bone in such way as to produce one or more guided wave modes within the bone, and the signals emerging from the bone are stored and analysed to determine the propagation characteristics of the guided wave/s. These measured guided wave propagation characteristics are then processed to obtain estimates of desired bone properties such as cortical thickness, bone density and bone elastic constants. The invention also comprises an ultrasound arrangement with movable transducers.

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## A METHOD AND DEVICE FOR THE NON-INVASIVE ASSESSMENT OF BONES

### Field of the invention

The invention relates to a method and a device for assessing human bones in vivo using ultrasonic waves. The invention deals with the production and detection of guided ultrasonic waves propagating within a bone, and with the determination of bone properties from measured guided wave parameters.

### Background of the invention

The so-called axial transmission technique has been used to assess long bones for over four decades (see, for example, Gerlanc et al, Clin. Orthop. Rel. Res. 1975;111:175-180). With this method, an ultrasonic pulse is transmitted along the long axis of a bone (typically the tibia) from a transmitter to a receiver and the velocity is estimated from the transit time of the first arriving signal and the propagation distance. To account for the effects of overlying soft tissue, either a multiple transmitter/receiver configuration can be used, or transit time can be determined as a function of distance as one transducer is moved relative to the other. At least two commercial clinical devices for bone assessment using axial ultrasound transmission have been produced: the Soundscan 2000/Compact (Myriad Ultrasound Systems Ltd., Rehovot, Israel) operating at 250 kHz, and the Omnisense (Sunlight Medical Corp., Rehovot, Israel) operating at 1.25 MHz (see patent no. WO 99/45348). A recent investigation by Camus et al (J Acoust. Soc. Am. 2000;108:3058-3065) into the axial transmission technique indicated that, under certain conditions, the first arriving signal can correspond to a lateral wave (or head wave) propagating along the surface of the solid at the bulk longitudinal velocity. The conditions under which lateral waves were observed included an appropriate measurement geometry (in terms of the separation of the transducers and their distance from the surface), an approximately point-like transmitter and receiver (spherical wavefronts), and the use of wavelengths less than the thickness of the solid layer. Tibial ultrasound velocity values measured in vivo are comparable to, or slightly lower than, in vitro measurements of the axial longitudinal wave velocity in excised human cortical bone specimens. However, there is experimental evidence indicating that the velocity of the first arriving signal is lower than the longitudinal velocity when the wavelength is greater than the bone thickness. Simulation studies show similar trends, and indicate that the waves contributing to the first arriving signal change as the sample becomes thinner. Clinical evidence for such thickness effects is, as yet, inconclusive, but this may be due to differences in the ultrasonic frequencies used by the different commercial systems, or other methodological factors.

Tibial ultrasound velocity measured using current commercial devices correlates with tibial bone mineral density (BMD), and, to a lesser extent with BMD at other skeletal sites (see, for example, Foldes et al. Bone 1995; 17:363-367), and also reflects cortical bone elastic modulus. However, tibial ultrasound is a poor discriminant of osteoporotic fracture, and is only weakly correlated with femoral strength and BMD. There are a number of reasons why current tibial ultrasound measurements may be sub-optimal in terms of their sensitivity to relevant bone properties. Waves propagating at the bone surface may preferentially reflect the material properties of bone in the periosteal region. In osteoporosis, cortical bone changes occur primarily in the endosteal region. The porosity of endosteal

bone increases leading eventually to endosteal resorption, "trabecularisation", and thinning of the cortex. In addition, recent nanoindentation studies suggest there may be differential changes with aging in the elastic properties of periosteal and endosteal bone purely at the material level. Ultrasonic methods that target these known pathological changes are likely to prove more valuable clinically. A further concern is that if density and elasticity both exhibit a parallel change, for example as a result of a change in porosity, ultrasound velocity may not be altered because the two effects tend to cancel out (since longitudinal velocity varies as the square root of elasticity divided by density). These considerations suggest that any improved ultrasonic method for cortical bone assessment should be sensitive to one of more of the following factors: a) reduced cortical thickness, b) structural changes in the endosteal region, such as increased porosity, and c) changes in bone density and elasticity at the material level, ideally independently of each other.

In general, little consideration has been given to the possibility of using different types of ultrasonic waves in long bones. One exception has been work reporting low frequency ultrasonic measurements of "surface wave" velocity in the tibia, mapping the spatial variation in velocity (Jansons et al. *Biomaterials* 1984;5:221-226). However, since pure surface waves only exist in structures that are much thicker than the wavelength, it is likely that these researchers were actually measuring a guided wave mode reflecting both bone thickness and material properties. Guided waves propagate within bounded or layered media, and their characteristics are determined by the geometrical and material properties of the structure and of the surrounding media. They arise from the reflection, mode conversion and interference of longitudinal and shear waves within the structure (Victorov L.A. *Rayleigh and Lamb Waves*. New York, Plenum, 1967). Ultrasonic guided waves are quite widely used in engineering non-destructive testing for the assessment of plates, tubes and more complex structures.

### **Summary of the invention**

The main object of the present invention to provide a method capable of measuring the velocity of at least two ultrasonic waves propagating in a bone at the same time, where at least one of said waves is a guided wave according to Lamb wave theory. This object is achieved through a method and the device as defined in the accompanying claims. The invention makes use of the well known Lamb wave theory for guided waves in solid elastic plates, demonstrating for the first time how these guided waves can be applied for the non-invasive assessment of bones.

The cortex of human long bones essentially comprises a curved plate of solid bone, and should be capable of supporting the propagation of guided waves similar to Lamb waves. Lamb waves are two-dimensional elastic waves that propagate in a free solid elastic plate of finite thickness in a vacuum. They arise from the multiple reflection and mode conversion of longitudinal and shear waves from the upper and lower surfaces of the plate. They exist in the form of resonant modes where the combination of frequency and phase velocity corresponds to standing waves in the thickness direction. For symmetric modes, identified as S0, S1, S2, etc., the motion is symmetric about the mid-plane of the plate, whereas in antisymmetric modes (A0, A1, A2, etc.) the motion is antisymmetric. The behavior of each mode is described by a dispersion curve which characterises the variation in phase velocity with frequency. All but the two fundamental modes, S0 and A0, have a cut-off frequency.thickness product ( $F.d$ ). Thus for very low frequencies, or for very thin plates, only the fundamental (S0 and A0) modes can be excited. In these conditions, the

phase velocity of the S0 wave approaches that predicted by 'thin plate' theory, given by an equation analogous to the bar wave equation (Graff K.F. Wave Motion in Elastic Solids. New York, Dover, 1991). With increasing  $F.d$ , the velocities of all of the Lamb modes asymptotically approach the Rayleigh wave velocity. Lamb wave terminology is often also used to describe wave propagation in plates loaded by an external medium such as a fluid. The boundary conditions are modified by the presence of a surrounding medium and the characteristics of Lamb waves in a fluid immersed plate are different from those of Lamb waves in a free plate. For example, if the phase velocity of the fluid is close to the phase velocity of a Lamb mode, the mode continuously radiates into the fluid and therefore its attenuation is high. In this document, the term "Lamb wave" is used in its general sense to apply to guided waves propagating in plates, tubes and other geometries where there exists a solid layer, and also to cases where the solid layer is bounded by a surrounding fluid medium.

Another object of the present invention is to provide a method for exciting ultrasonic waves in a bone using low frequency small diameter contact transducers so as to preferentially produce guided waves in the bone. By measuring at low frequencies, the velocity of the first arriving wave has enhanced thickness-dependence, with a velocity tending towards that of the fundamental symmetric Lamb wave. In effect, the first arriving signal can be considered to be a guided wave in these circumstances. Low frequency small diameter transducers behave as approximately point-like transmitters and receivers, radiating energy in all directions, and coupling into additional guided waves that arrive after the first arriving signal.

Yet another object of the present invention is to provide a method for maintaining a near constant contact force between the ultrasound transducer and the limb. During in vivo measurements some movement of the patient is to be expected and this may lead to variations in contact force unless corrected for. Variations in contact force may have an adverse effect on the coupling of acoustic energy into the bone and may lead to errors in the measurements.

Further object of the present invention is to provide a method for analysing the data from an axial transmission scan in the form of an  $(r,t)$  or (distance, time) diagram, from which different propagating waves can be identified and their velocities determined from the slope of lines fitted to the waves. By using this approach, waves arriving after the first (fastest) signal can be detected and measured.

Further object of the present invention is to provide a method for enhancing the discrimination and measurement of guided waves through the use of spectral analysis applied to the received signals. This includes calculating the frequency spectrum of the received signal, calculating the spectrogram (time-frequency analysis), and performing two dimensional Fourier transform on the  $(r,t)$  data array (frequency-wavenumber analysis). Additionally, or alternatively, the received signals may be filtered to enhance or reduce specific frequency components. Additionally, or alternatively, the excitation signal sent to the transmitting transducer may be a specified arbitrary function chosen in the knowledge of the transducer frequency response so as to produce an output signal with particular characteristics.

Further object of the present invention is to provide a method for employing an array of transducers so that scanning of the receiver can be performed electronically by using different transducer elements, or combinations thereof, as

receivers. In this way, the received signal can be measured as function of transmitter-to-receiver distance, and an (r,t) diagram formed as described earlier, but with the advantage that no moving parts are involved.

Further object of the present invention is to provide a method for employing a comb transducer consisting of a set of transducer elements with constant spacing between the elements. Either transmitter, receiver or both may be a comb transducer. The comb transducer excites (or detects) guided waves with a constant wavelength determined by the spacing of the elements. By choosing appropriate frequencies, selected guided waves can be produced and measured in the bone.

Further object of the present invention is to provide a method for coupling energy from ultrasound transducers into guided waves in the bone by use of transducers placed at an angle to the bone and coupled to the limb through a fluid or solid medium. Using such a method guided waves with known phase velocity may be preferentially produced, this phase velocity being determined by the angle and the velocity in the coupling medium, through Snell's law. The transducers may be in contact with the bone with a small amount of gel used to maintain acoustic coupling, or the transducers may be some distance above the limb with the acoustic signal consequently travelling some appreciable distance through the coupling medium.

In one embodiment of the invention two transducers are used in a reflection configuration at a specified angle of incidence for the transmitter (and the same angle of reflection for the receiver) to excite and detect guided waves at a single point on a bone. Minima in the reflected frequency spectra correspond to energy being coupled into guided waves in the bone. The angle of incidence/reflection may be varied to obtain data over a range of angles. The angle can be related to phase velocity through Snell's law, and hence dispersion curves may be determined. The method may be implemented using either broadband pulses, tonebursts or continuous waves. By rotating the transmitter/receiver about an axis normal to the bone surface, the anisotropy in the plane of the bone layer may be assessed.

In another embodiment of the invention, a single transducer is pulsed and used both as transmitter and receiver. Thus, the transducer is aligned at right angles to the bone surface and is operated in pulse-echo mode. The signals reflected from the bone are obtained at normal incidence. The time difference between the reflection from the upper and lower bone surfaces is used to estimate bone thickness. This time difference may be determined in the time domain. Alternatively the time difference may be determined in the frequency domain, since the frequency spectrum of the composite received signal will be modulated with a period of  $dF = 1/t$ , where  $t$  is the time delay between the two reflected signals. The estimated thickness may be calculated as  $d = v(t/2)$  where  $v$  is the sound speed in bone in the radial direction, which may be taken from the literature (typically 3300 m/s).

In another embodiment of the invention, measured guided wave acoustic parameters, such as the velocities of different guided wave modes and/or the velocity of specific modes at different frequencies, are used as input data to a mathematical inversion algorithm. The outputs from this algorithm are estimates of bone properties of interest, potentially including bone thickness, bone density, bone elastic constants (elastic modulus, Poisson ratio). The mathematical inversion algorithm is based on an iterative process using analytical guided wave theory. Initial estimates of the bone properties are used to calculate guided wave acoustic parameters from guided wave theory. These are com-

pared with the measured acoustic parameters, and then the initial estimates of bone properties are adjusted in such a way as to reduce the overall error, and the process is repeated until the error becomes acceptably small. Additionally or alternatively, an artificial neural network may be used to obtain estimates of bone properties from the measured acoustic parameters. Additionally, or alternatively, an estimate of the bone thickness obtained using said forementioned reflection measurement may be used as an additional input to the mathematical inversion algorithm.

Further object of the present invention is to provide a method for detecting and localising regions with abnormal bone properties. To achieve this guided wave measurements may be made at a number of locations in the bone so that regions with abnormal properties may be detected. One application would be to detect the presence of so-called stress fractures within the bone. Stress fractures are often very difficult to observe on x-ray images because of their small size, but they will have a large effect on Lamb wave propagation through the bone. In addition, measurements may be made at a region of particular interest, for example, at the site of a healing fracture, in order to monitor changes in bone properties.

#### **A short description of the drawings and tables**

Figure 1. Schematic diagram of the axial transmission measurement system for a preferred embodiment of the invention.

Figure 2. Leg support on the chair and transducers in contact with the patient's leg.

Figure 3. Transducer units seen in front.

Figure 4. Preferred transducer unit with an actuator.

Figure 5a. Phase velocity of guided modes, theoretical Lamb wave dispersion curves in acrylic plates.

Figure 5b. Group velocity of guided modes, theoretical Lamb wave dispersion curves in acrylic plates.

Figure 6. An (r,t) diagram for a 3 mm thick acrylic plate.

Figure 7. Experimental and predicted data for acrylic plates.

Figure 8. An (r,t) diagram for a human tibia measured in vivo.

Figure 9. Table showing ultrasound and bone mineral density results in normals and osteoporotics.

Figure 10a - c. Alternative transducer configurations for other embodiments of the device.

Figure 11. Schematic diagram of the guided wave reflection measurement system for a preferred embodiment of the invention.

Figure 12. Mechanism for transducer movement for purposes of reflection measurements.

Figure 13. Schematic diagram of the estimation of bone properties from measured acoustic parameters in a preferred embodiment of the invention.

#### **Detailed description of preferred embodiments**

Figure 1 illustrates the measurement system of the first embodiment of the invention. A pair of non-focused contact transducers 12, 13 with a center frequency of approximately 200 kHz and a diameter of 6 mm are used. The transducers are orientated perpendicularly to the surface of the object 20 to be measured and a coupling medium, which may be ultrasonic gel, a soft plastic, or some other fluid or solid medium or media is applied. The transmitter is kept

at a fixed axial position during the measurement, but the receiver is moved progressively under computer control 34, 37, with the transmitter-receiver distance increased typically from  $r_0 = 20$  mm to  $r = 50$  mm by 0.5 mm steps. The main movement axis is automated by a stepper motor 30, 31 controlled linear actuator with a maximum line accuracy of 0.015 mm (RK Rose+Krieger trapezoid linear unit 303300 30 driven by bipolar Superior Electric stepping motor, model KLM091F13 with stepping module 430-T). Transducer contact pressures are determined by the load cells 14, 15 (Sensotec Inc, model 31). The DC readings are amplified and A-D converted (National Instruments 7344) 38, 39. The transmitting transducer is excited by a square wave pulser 36 (Panametrics 5077PR) with an amplitude variable from 100 V to 400 V. Signals from the receiver are amplified with a custom-made charge amplifier 32 with 40 dB voltage gain and are then acquired by a digital oscilloscope 33 (National Instruments 5102) with sampling rate of 10 MSPS. The data acquisition is triggered by the pulser at a pulse repetition frequency (PRF) of 200 Hz. Software for data acquisition and analysis is implemented using LabView (National Instruments) with Matlab also used for some analyses.

Figure 2 shows the leg support on the chair. The first embodiment of the invention includes a chair (not shown) with an attached leg support 2 and a ultrasound scanning device mounted on the leg support 2. The scanning device has

- two transducers 12, 13 (transmitter and receiver), where one transducer is fixed during the measurement and one moves along the axis of the limb being measured, and
- means for adjusting the position of the moving transducer automatically, and
- means for adjusting the vertical position of the transducers relative to the limb surface using actuators so as to achieve a specified contact force, and
- means for detecting the forces in the the tip of each transducer (contact pressures), and
- means for acquiring the received signals as function of transducer separation, producing an (r,t) diagram from input data and analysing it in order to calculate the wave speeds, and, optionally, other acoustic parameters such as attenuation. In Fig. 2 transducers 12, 13 are shown separately without a supporting slide mechanism, which is further supported by the chair 1. The leg support comprises the pillows 2.1, 2.2 and 2.3 and the frame 3 supporting them and a slide mechanism of the transducers.

Alternatively both transducers can be moved, or a fixed transmitter may be used with at least two receivers which may move, or a fixed array of transducers may be used each of which may function as both transmitters and receivers.

Or fixed transmitter and at least two receivers, or fixed transducer array, or movement (scan or array) around the leg in order to detect one wave with low velocity (lower than the velocity of sound of longitudinal waves in bone).

Figure 3 shows the transducer units seen from the front and in contact with a tibia. Each transducer 12, 13 is carried by a slide 10, 11. The transducer unit includes a transducer holder 18, 19 a force sensor 14, 15 and nuts 23, 24, which secure the transducers to the slides 10, 11. Both slides have manual positioners (not shown) for the vertical adjustment along the vertical guides 10.1, 11.1. Each one is secured to another slide moving along a horizontal guide by a stepping motor (not shown).



Figure 4 shows an advanced transducer unit. The unit includes a transducer holder 18, a force sensor 14 (a precision miniature load cells, Sensotec Inc, model 31), a connection sleeve and an actuator 21 (H.S.I. miniature linear actuators model 20561-05 with a stroke of 12.7 mm). The actuator allows the transducer position to be altered to maintain a specified contact force with the limb. The unit is secured to a slide by the lugs 21.1.

Figures 5a and 5b show theoretical Lamb wave dispersion curves for the first four symmetrical (S0-S3) and anti-symmetrical (A0-A3), guided modes in acrylic plates: Fig. 5a) phase velocity, Fig. 5b) group velocity. The horizontal axis is the frequency, thickness ( $F.d$ ) product. These curves were calculated using the Rayleigh-Lamb equation assuming a longitudinal velocity of 2750 m/s and a shear velocity of 1375 m/s for acrylic. Lamb waves are two-dimensional elastic waves that propagate in a free solid elastic plate of finite thickness in a vacuum. They arise from the multiple reflection and mode conversion of longitudinal and shear waves from the upper and lower surfaces of the plate. They exist in the form of resonant modes where the combination of frequency and phase velocity corresponds to standing waves in the thickness direction. Each continuous curve in Figs. 5a and 5b represents a guided wave mode. From these dispersion curves it can be seen that all but the two fundamental modes, S0 and A0, have a cut-off frequency, thickness product. Thus for very low frequencies, or for very thin plates, only the fundamental (S0 and A0) modes can be excited. In these conditions, the phase velocity of the S0 wave approaches that predicted by 'thin plate' theory, given by an equation analogous to the bar wave equation. At high  $F.d$  values the velocities tend asymptotically toward the Rayleigh velocity. Lamb wave terminology is often used to describe wave propagation in plates loaded by an external medium such as a fluid. The boundary conditions are modified by the presence of a surrounding medium and the characteristics of Lamb waves in a fluid immersed plate are different from those of Lamb waves in a free plate. For example, if the phase velocity of the fluid is close to the phase velocity of a Lamb mode, the mode continuously radiates into the fluid and therefore its attenuation is high.

Figure 6 shows a so-called (r,t) diagram arising from a measurement made on a 3mm thick acrylic plate. The (r,t) diagram is produced by plotting the received radio frequency (RF) signals as a function of distance  $r$ , giving a (r,t) diagram. Each received RF waveform was plotted as a horizontal line in which absolute amplitude is mapped to a grey scale value, with the maximum amplitude corresponding to white. These horizontal lines are stacked vertically to give a so-called (r,t) diagram in which the horizontal axis was time (t) and the vertical axis was distance (r). From the (r,t) diagrams propagating wave/s are visualised, and, by fitting a line to the peaks within a wave packet, velocities are measured. Two waves are observed consistently in the (r,t) diagrams shown and, because of their different characteristics, different methods are adopted to determine the velocity of each. The first arriving signal (Wave 1) is generally of a low amplitude and relatively non-dispersive, and is tracked by using a thresholding approach set at 25% of the first peak maximum. This value is selected empirically to prevent the tracking failing due to noise. Tracking of the slower wave packet (Wave 2) is more difficult due to interference from other components in the received signals. A semi-automatic approach is adopted in which the user selects a peak in the first RF line within the slower wavepacket from which to begin tracking. The software then searches forward in the next RF line using a relatively small time window to minimise the chance of jumping to another, incorrect, peak. This process continues through all of the RF lines, and then a straight line is fitted to the points. Errors can be corrected manually by the user and a new fit made. The phase velocities of the first and second waves are then calculated as the slopes of the linear fits to the points in the first and second wavepackets respectively.

Figure 7 shows the results of a series of measurements on acrylic plates. The theoretical predictions for the velocity of the fundamental symmetric (S0) and antisymmetric (A0) Lamb waves are also shown. The first arriving wave (Wave 1) propagated at the longitudinal velocity in thick plates, but in thin plates velocity decreased towards that predicted for the S0 Lamb wave. Hence, in thin layers measured at low frequencies, the first arriving wave can also be considered to be a guided wave. The slower wave (Wave 2) agreed closely with predictions for the Lamb A0 wave, leading to the conclusion that the second wave is indeed a Lamb A0 guided wave.

Figure 8 shows an (r,t) digram obtained from measurements on a human tibia in vivo in a normal healthy volunteer. Two distinct propagating waves are again observed as in the acrylic plates.

Figure 9 is a table of results of a pilot study in which ultrasound measurements were made in normal and osteoporotic subjects. Comparing the values in the healthy and osteoporotic subjects, significant differences were found only for the slower guided wave. In osteoporotics the velocity of the slower guided wave (Wave 2) was 15% lower than in normals. These results suggest that the velocity of the A0 guided wave (i.e. the second wave) is the best discriminant of osteoporosis.

Figures 10a, 10b and 10c show alternative transducer configurations. The transducers 16, 17 may be coupled directly to the skin at normal incidence using gel 40, 42 (or liquid 41 in Fig 10b) to assist coupling. Alternatively they may be placed at a specified angle to the skin but still in direct contact, with gel used to maintain an acoustic path. Alternatively the transducers may be placed some distance above the skin with a coupling medium or media, which may be solids or fluids, placed between the transducer and the skin. The transducers may be angled or kept at normal incidence. By placing the transducers at an angle to the bone surface (with holders 43), particular guided wave modes may be preferentially excited and measured. The angle may be varied during a measurement. Alternatively, an array of transducers may be employed, where each transducer element can function either as a transmitter or a receiver. With such an array, the received signal may be obtained as a function of transmitter-receiver distance without any mechanical scanning. In addition, under electronic control such an array may be used for beam forming and beam steering, allowing the angle of the "transmitter" and "receiver" to the bone surface to be varied.

Figure 11 shows schematically another embodiment of the invention in which guided waves are measured with two transducers 16, 17 using a reflection approach. A container 46 contains liquid as coupling medium 45. Transmitter and receiver are configured so that the angle of incidence is equal to the angle of reflection. The transmitter emits an ultrasonic signal, which may be a pulse, toneburst or continuous waves, and the signal reflected from the bone surface is detected by the receiver. At a given angle, the received signal is a function of frequency with minima at frequencies corresponding to instances where energy is coupled into a guided wave mode in the bone layer. The angle of incidence ( $\theta$ ) can be related to the phase velocity ( $c$ ) of guided waves in the bone using Snell's Law, as follows,

$$c = c_1 / \sin \theta$$

where  $c_1$  is the velocity of sound in the coupling medium. Hence by acquiring data over a range of angles, it is possible to detect guided waves and to characterise them in terms of phase velocity and frequency. Dispersion curves similar to those in Figure 5 can be produced.

Figure 12 shows an embodiment for a mechanism for varying the angle and orientation of a pair of transducers 16,17 whilst ensuring that the angle of incidence is equal to the angle of reflection at all times and that the transducer beam axes coincide at a point. This point should correspond with the position of the bone surface. The vertical position of the transducers may be varied to find the bone surface. A parallelogram 47 has four pieces jointed together and the upper joint moves along a vertical guide 48. The transducers 16, 17 are secured onto the lower pieces.

Figure 13 shows schematically how the acoustic measurements may be used as input data to a mathematical algorithm for estimating specific bone properties of interest.

**Claims**

1. A method for the non-invasive assessment of bones, in which method there are the following stages,
  - an ultrasound signal is directed onto the bone, propagates within the bone, and is emitted from the bone,
  - the ultrasound signal emitted from the bone is detected and recorded,
  - at least one bone property is calculated with a chosen method from the recorded signals,characterized in that
  - one or more modes of Lamb waves are detected, these modes having a relationship with the said bone property or properties, and
  - the velocity of the detected wave mode or modes is measured, and
  - the bone property or properties are calculated from the measured velocity or velocities.
2. Method according to claim 1, wherein the detected Lamb wave mode is the lowest asymmetric mode, i.e. the A0 mode.
3. Method according to claim 2, wherein
  - two wave modes are detected and their velocities are measured and recorded one mode being the said A0 mode and other one the first arriving wave,
  - a image of the amplitude of the received signal as a function of time and transducer separation is produced from the recorded signals,
  - at least two propagating waves are identified from the scanned image
  - velocities of propagating waves are determined from the slopes of a lines fitted to the waves in the image.
4. Method according to claim 3, wherein
  - the arriving signal is measured at least at two different transmitter-receiver distances,
  - the bone is scanned for a chosen length by sending signals in at one point and receiving the responses at another point,
  - either the transmitting or receiving point, or both, are moved, continuously or in steps, during the measurement,
  - received signal is recorded from a number of differing transducer separations during the scan.
5. Method according to claim 3 or 4 wherein the contact pressure of the transducer is controlled by detecting the axial force and moving the transducer respectively.
6. Method according to claim 3 or 4 wherein the transmitting and/or the receiving transducer are placed at an angle to the bone surface and the ultrasonic beam travels to and from the bone through an intervening coupling medium.
7. Method according to one of claims 3 - 5 wherein the angle of the transducers to the bone can be changed during the measurement to identify particular angles favourable to the production and detection of specific types of waves.

8. Method according to claim 3 wherein the transmitting and/or receiving transducers are arrays of individual transducers that may be electronically controlled to achieve scanning without mechanical movement and/or to enhance the production and detection of specific waves, for example through electronically forming and steering the acoustic beam.
9. Method according to one of claims 1 - 3 wherein transmitting and/or receiving transducers are comb transducers composed of several transducer elements spaced a constant distance apart, so that they excite and detect guided waves with a constant wavelength determined by the spacing of the elements.
10. Method according to claim 3 wherein a Fourier transform is performed on the received signals to facilitate discrimination and measurement of one or more waves.
11. Method according to claim 3 wherein time-frequency analysis is performed on the received signals to facilitate discrimination and measurement of one or more waves.
12. Method according to claim 3 wherein a 2-dimensional Fourier transform is performed on the received signals as function of time and transducer separation to facilitate discrimination and measurement of one or more waves.
13. Method according to claim 3 wherein filtering of the received signals is performed to facilitate discrimination and measurement of one or more waves.
14. Method according to claim 3 wherein a specified excitation signal is sent to the transmitting transducer in order to modify the frequency spectrum of the emitted signal and hence facilitate discrimination and measurement of one or more waves.
15. Method according to claim 3 wherein the phase velocity of a wave is determined by fitting a line to points of constant phase (e.g. peaks or zero-crossings) within a wave packet.
16. Method according to claim 3 wherein the group velocity of a wave is determined by fitting a line to the amplitude envelope of a wavepacket.
17. Method according to claim 1 wherein the attenuation of a wave is determined from the decrease in amplitude of that wave with increasing transducer separation.
18. Method according to claim 1 wherein the production, detection and measurement of ultrasonic Lamb waves in the bone at a single location comprises:
- a transmitting transducer and receiving transducer configured for reflection measurements such that the angle of incidence of the beam is always equal to the angle of reflection, and both transducers are directed towards, and move around, a common axis on the bone surface,
  - a means for varying the angle over a selected range

- a means of measuring the received signal amplitude as a function of angle and of frequency
- a means of identifying minima in the reflected signal, which correspond to the presence of a Lamb wave mode in the bone, and hence, by relating angle to phase velocity through Snell's Law, characterizing Lamb wave mode or modes in terms of phase velocity and frequency.

19. Method according to one of claims 1-3 wherein a low frequency of ultrasound is used such that the first arriving signal detected corresponds to the fundamental symmetric Lamb wave (S0 wave) in the bone.

20. Method according to Claim 1 or 2 wherein a single transducer is aligned at right angles to the bone surface and is operated in pulse-echo mode, transmitting an ultrasonic signal to the bone and detecting the reflected signal from the bone and the time difference between the reflection from the upper and lower bone surfaces is determined, and is used to estimate bone thickness.

21. Method according to one of claims 1-3 wherein bone properties are estimated from Lamb wave measurements using a mathematical algorithm, comprises

- the calculation of Lamb wave parameters from a set of assumed bone properties using analytical Lamb wave theory,
- comparison of the calculated Lamb wave parameters with the measured Lamb wave parameters, and derivation of an error parameter representing the difference between the two,
- adjustment of the initial estimates of bone properties in such a way as to reduce the error parameter,
- repeated iteration of this process until the error parameter becomes acceptably small, the values of the bone properties then being taken as the best estimates of the true bone properties.

22. Method according to one of claims 1-3 wherein bone properties are estimated from from Lamb wave measurements using an artificial neural network, comprises

- use of the measured Lamb wave parameters as input data for an artificial neural network whose outputs correspond to selected bone properties
- training of said artificial neural network with experimental data from a range of bone phantoms and real bone samples of varying physical properties.

23. Method according to claims 1 or 2 wherein measurements are made at a number of locations within a bone so as to identify and characterise regions of abnormal bone properties.

24. Device for the non-invasive assessment of bone, which device comprises

- two transducers (12, 13), one being the transmitter (16) and one being the receiver (17), where one transducer (12) is fixed and one (13) is assembled on a slide member (11) gliding in a guide, and
- means (30, 31) for moving the slide member with the transducer, thus moving the transducer over the surface of the bone (20) or the limb,
- the transmitter (16) is adapted to send an ultrasonic signal into the bone (20),
- the receiver (17) is adapted to detect waves propagating within and emitted from the bone (20),

- means (32, 33) for measuring and recording the received signals,
- means (34) for calculating at least one bone property with a chosen method from the recorded signals,

characterized in that the device comprises also

- means (21) for adjusting the transducers (12, 13) onto the limb or bone (20) with a chosen force (preferably 50-300 g), and,
- means (14, 15) for detecting the forces, ie. contact pressures, at the tip of each transducer (12, 13)

25. Device for the non-invasive assesment of bone, which device comprises

- two transducers, one being the transmitter (16) and one being the receiver (17), where both transducers can move about, and are aligned towards, a common axis that lies on the bone surface, and,
- means (47, 48) for moving the transducers about said common axis such that the angle of incidence is always equal to the angle of reflection, and,
- means ( 45) for coupling the ultrasonic signal from the transmitter to the bone and back to the receiver, and,
- the transmitter (16) is adapted to send an ultrasonic signal into the bone, and,
- the receiver (17) is adapted to detect the ultrasonic signal reflected from the bone, and,
- means for detecting and recording the received signals,
- means for calculating at least one bone property from the recorded signals.

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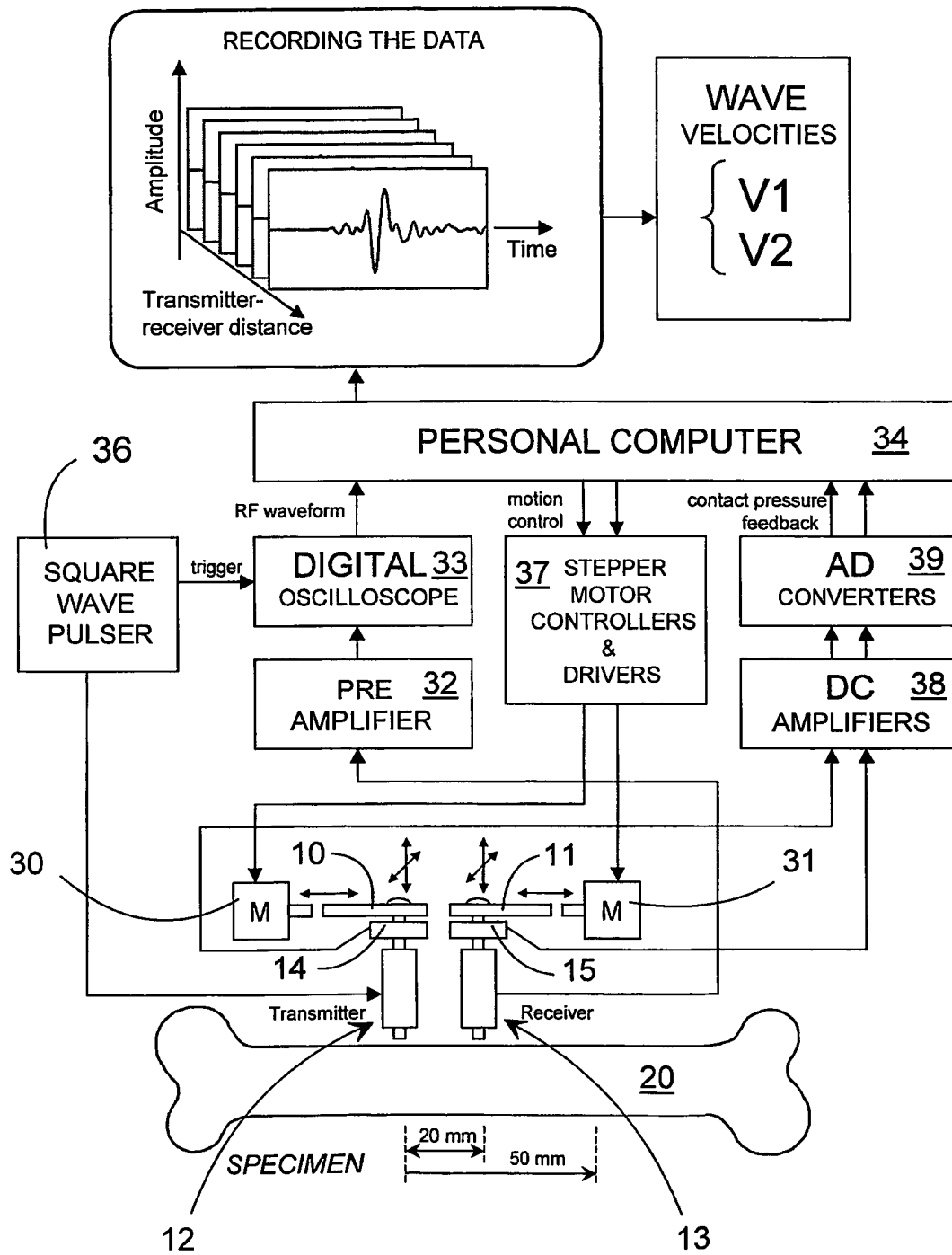


Fig.1



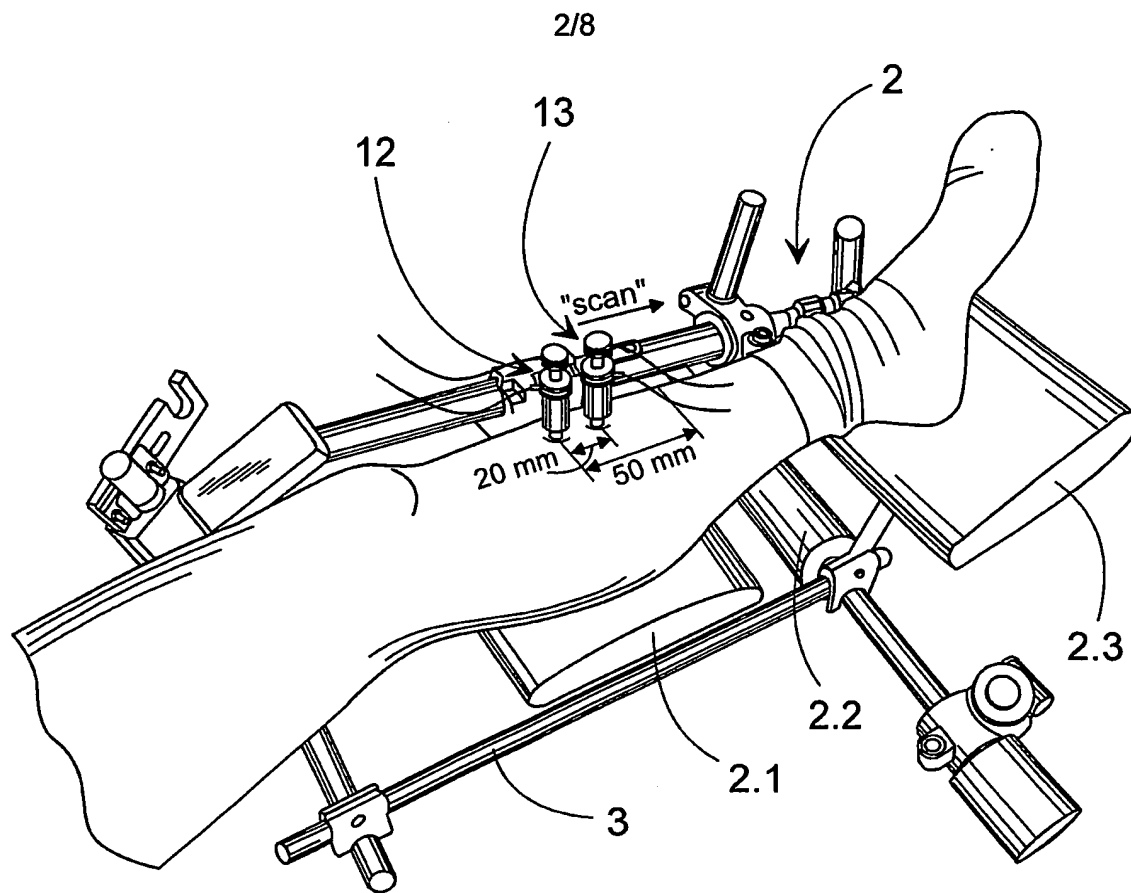


Fig. 2

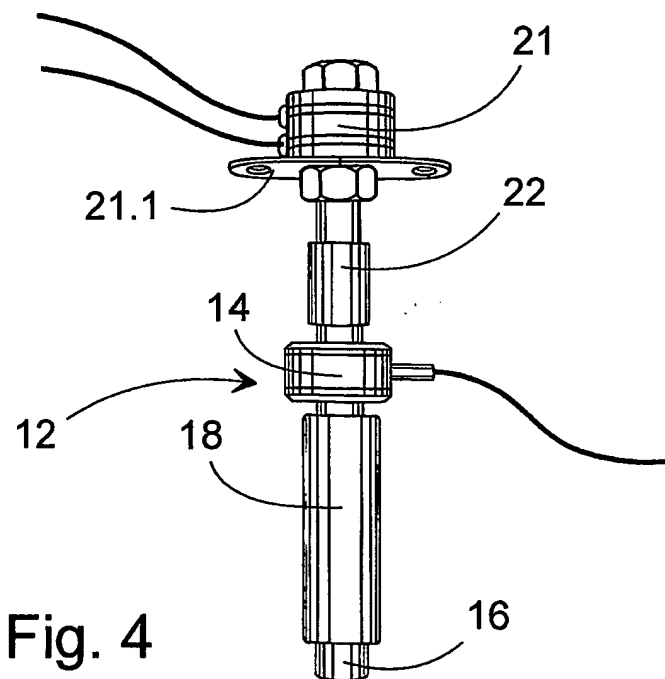


Fig. 4

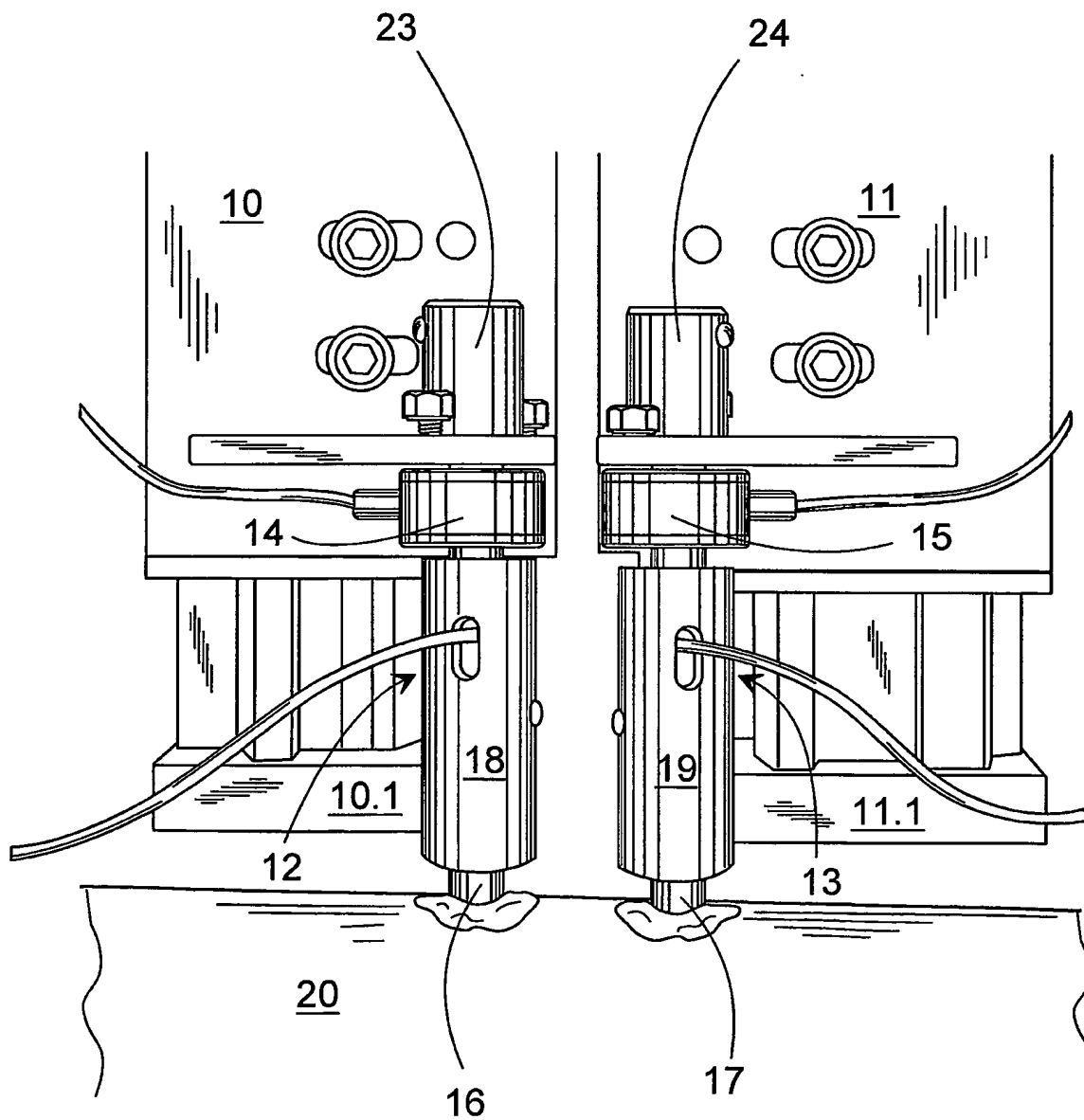


Fig. 3

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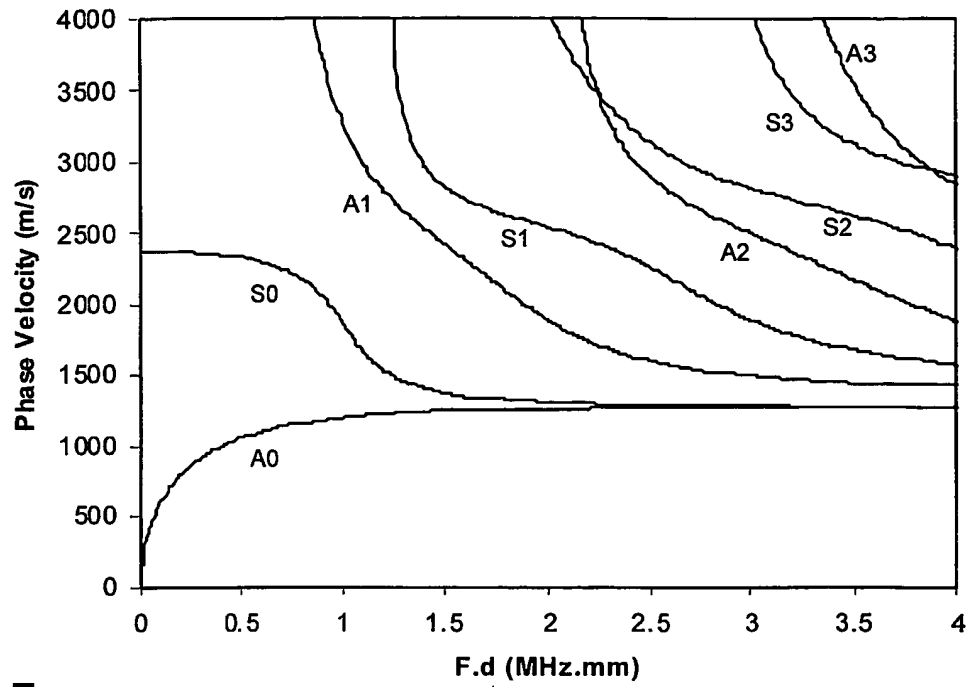


Fig. 5a

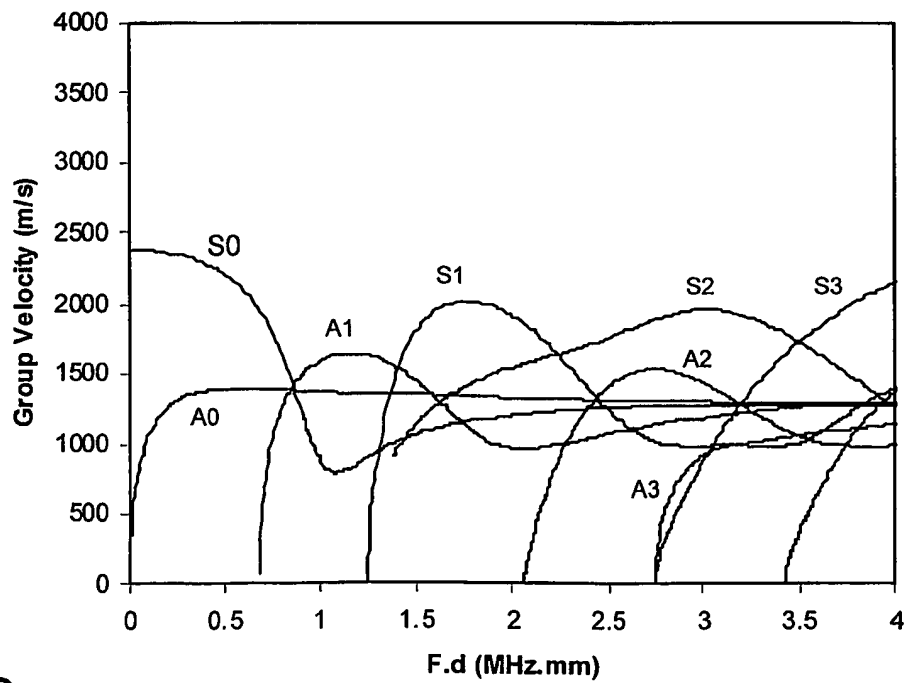


Fig. 5b

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Fig. 6

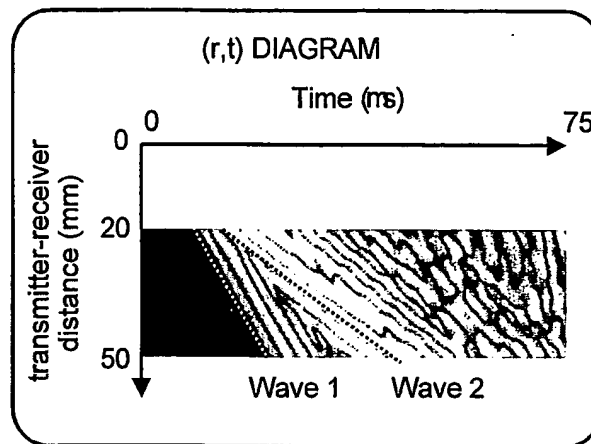


Fig. 7

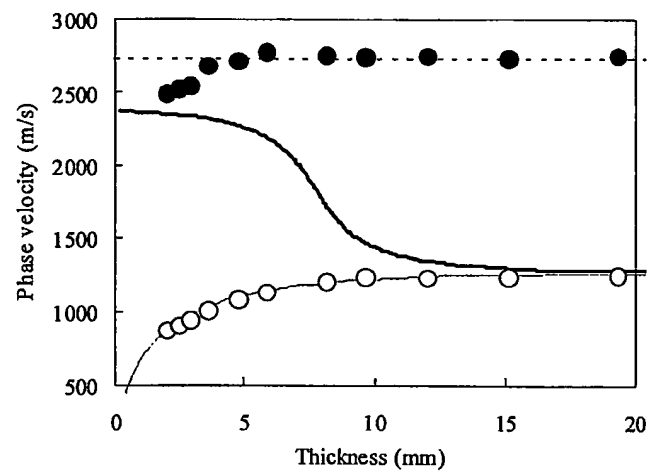
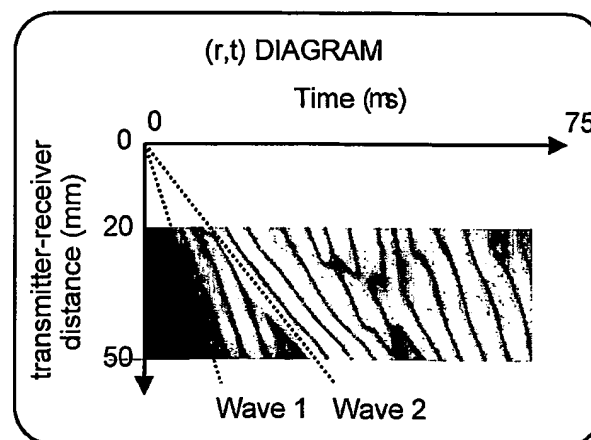


Fig. 8



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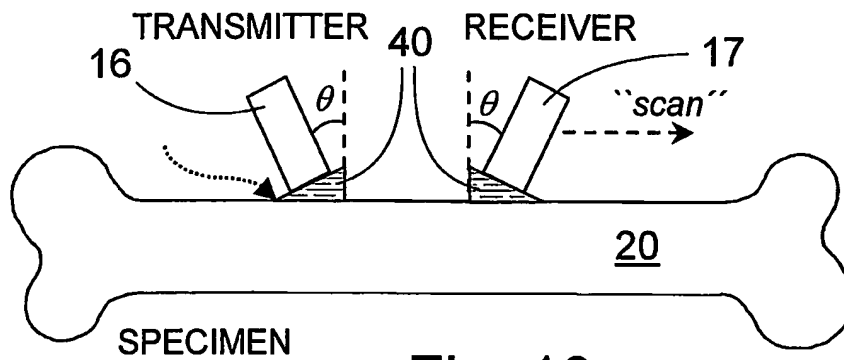


Fig. 10a

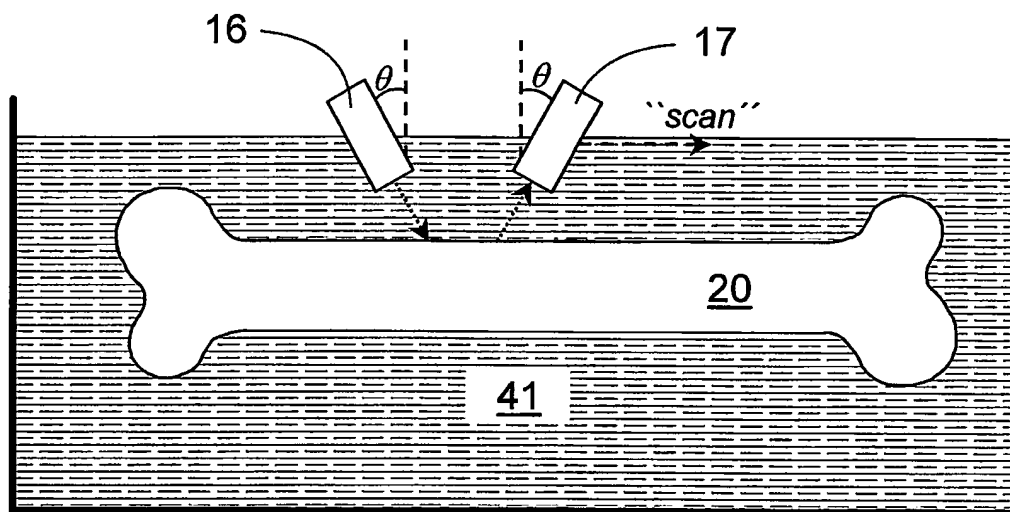


Fig. 10b

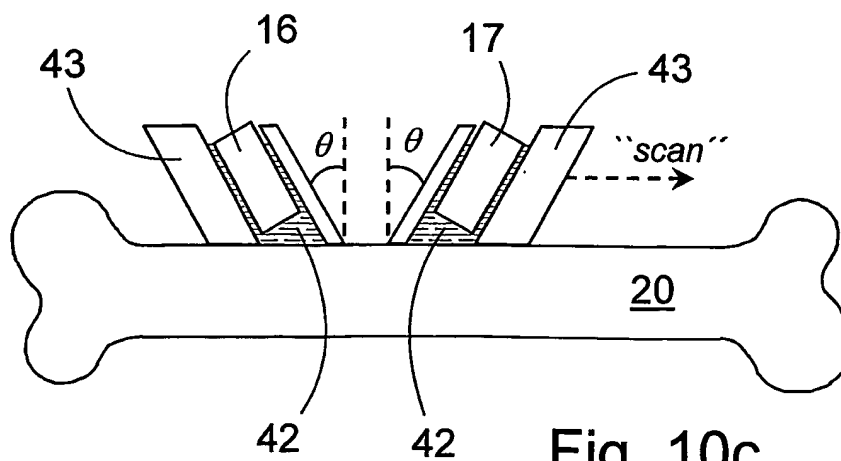


Fig. 10c

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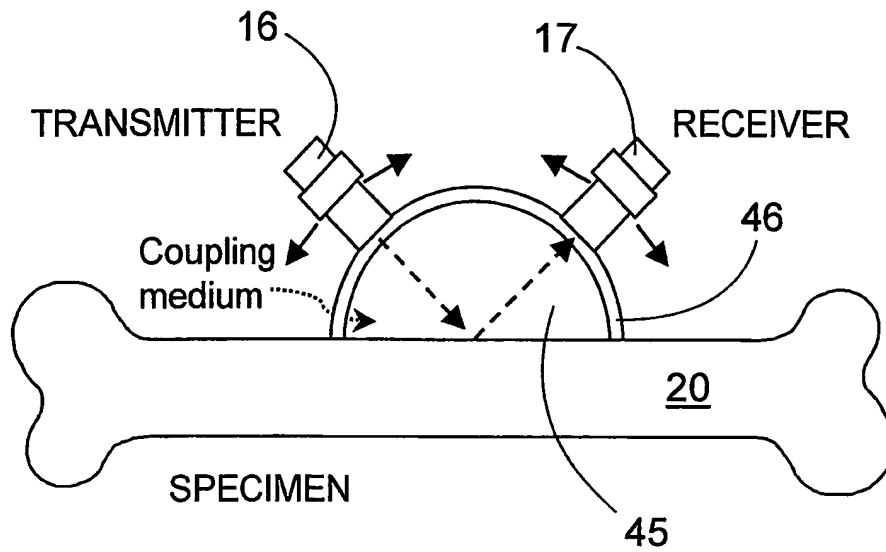


Fig. 11

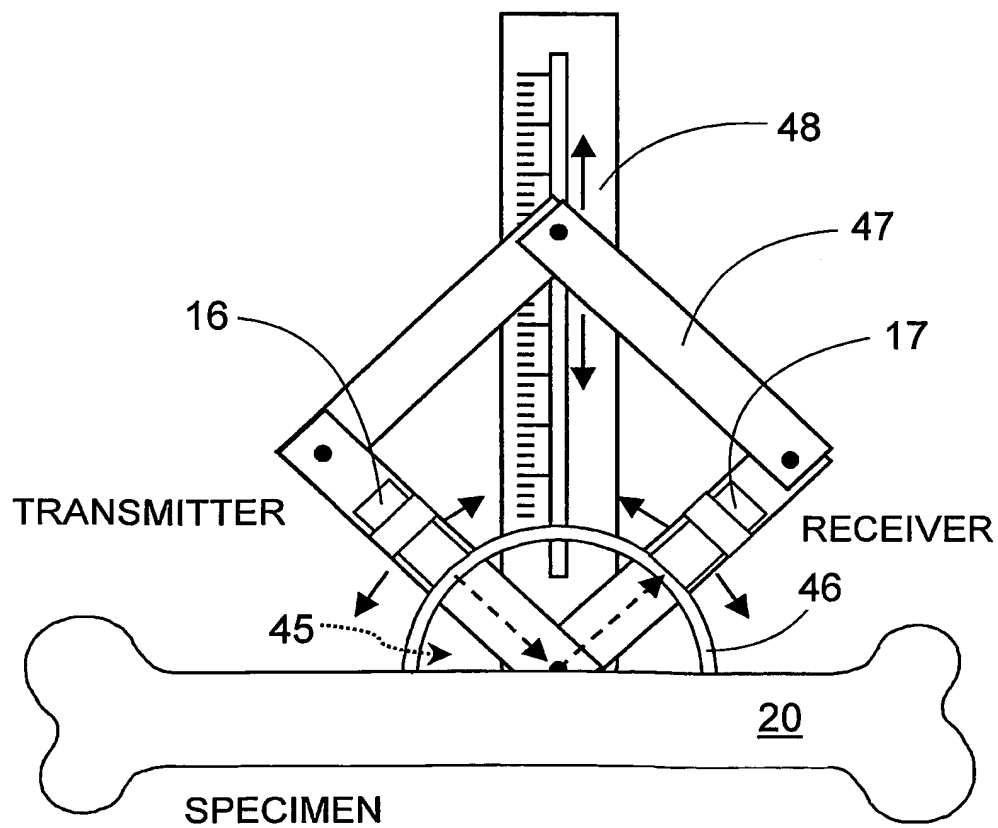
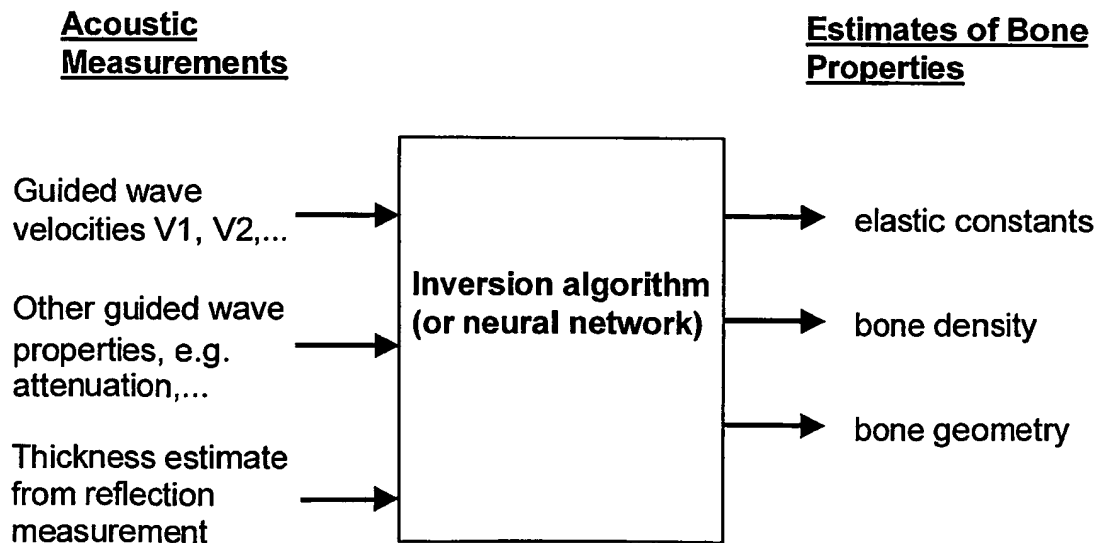


Fig. 12

**Table 1. Ultrasound and bone mineral density in normals and osteoporotics**

	Normal (n=8)	Osteoporotic (n=8)	Difference	p value
First wave velocity	3946 (190) m/s	3867 (165) m/s	-2%	ns
Second wave velocity	1615 (60) m/s	1399 (117) m/s	-15%	0.0004
Tibial SOS*	3800 (179) m/s	3771 (186) m/s	-1%	ns
Cortical BMD**	1018 (39) mg/ml	920 (111) mg/ml	-11%	ns

**Fig. 9****Fig. 13**

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 02/00957

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61B 8/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61B, A61N, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, INSPEC, MEDLINE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AHITE, D. et al. "New ultrasonic technique of bone characterization: preliminary study in vitro". INNOV. TECHN. BIOL. MED., 1998, Vol. 19, No. 4, pages 265 - 271, see page 268; figure 1 --	1-23
A	US 6322507 B1 (PASSE ET AL), 27 November 2001 (27.11.01), column 8, line 20 - line 25; column 9, line 40 - line 45, figure 10 --	1-23
A	LAUGIER, P. et al. "Quantitative Ultrasound for Bone Status Assessment". IEEE ULTRASONICS SYMPOSIUM, 2000, pages 1341 - 1350, see page 1345, column 1. --	1-23

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

28 March 2003

Date of mailing of the international search report

31-03-2003

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Sofie Carlsson /OGU

Telephone No. +46 8 782 25 00



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 02/00957

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	NICHOLSON, P.H.F. et al. "Guided ultrasonic waves in long bones: modelling, experiment and in vivo application". PHYSIOLOGICAL MEASUREMENT, 2002, Vol. 23, pages 755 - 768, see the whole document  --	1-23
A	GB 2257253 A (MCDONALD LANGTON, C.), 6 January 1993 (06.01.93), page 4, line 20 - page 5, line 3  --	24
A	SUH, J-K. F., et al. "An in situ calibration of an ultrasound transducer: a potential application for an ultrasonic indentation test of articular cartilage". JOURNAL OF BIOMECHANICS, 2001, Vol. 34, pages 1347 - 1353, see figure 1  --	24
X	US 5197475 A (ANTICH, P.P. ET AL), 30 March 1993 (30.03.93), column 5, line 52 - line 66, figure 2, abstract  -- -----	25

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/FI 02/00957**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-23  
because they relate to subject matter not required to be searched by this Authority, namely:  
see extra sheet
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

I: claims 1-23 relate to a method for assessment of bone with Lamb waves.

II: claims 24-25 relate to a device for assessment of bone with movable transducers.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

## Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/FI 02/00957

## Continuation of box I

Claims 1-23 relate to a diagnostic method performed on the human or animal body, namely a method for performing in-vivo measurements of bone characteristics that are indicative of cortical bone changes, such as osteoporosis. Thus the International Search Authority is not required to carry out an international search for these claims (Rule 39.1(iv)). Nevertheless, a search has been executed for claims 1-23.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No.

PCT/FI 02/00957

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
US	6322507	B1	27/11/01	AU	6365299 A	15/05/00
				EP	1123044 A	16/08/01
				IL	142447 D	00/00/00
				US	5952529 A	14/09/99
				WO	0024307 A	04/05/00
-----						
GB	2257253	A	06/01/93	GB	9112996 D	00/00/00
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US	5197475	A	30/03/93	AU	4062289 A	05/03/90
				CA	1313252 A	26/01/93
				DE	68927495 D,T	05/06/97
				EP	0428595 A,B	29/05/91
				US	5038787 A	13/08/91
				WO	9001296 A	22/02/90
				US	5228445 A	20/07/93
-----						